BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 53, NO. 10 DECEMBER 1977

VIBRATION ANALYSIS IN EXPERIMENTAL MODELS OF ATHEROSCLEROSIS*

IRA NATHAN, Ph.D., AND ANTHONY M. IMPARATO, M.D.

Department of Surgery
New York University Medical Center
New York, N.Y.

ALTHOUGH numerous investigators have associated atherosclerosis with abnormal blood flow, the specific characteristics of that flow which might be causal have not been identified.[1-8] Views regarding the initiating mechanism and the site of the initial cellular response which results in florid atherosclerosis have conflicted.

The earliest recognizable lesion appears to be intimal cellular thickening. Serial studies of the presumed first stage of atherosclerosis in experimental animals suggest that fragmentation of the internal elastic lamella, migration of smooth muscle cells from media to intima, and shedding of endothelial cells occur almost simultaneously to produce the characteristic intimal fibrous plaque. The predominant view now is that endothelial

*Presented as the First Harold Lamport Memorial Lecture of the Section on Biomedical Engineering of the New York Academy of Medicine November 9, 1976.

This research was supported in part by the Kahn Brothers Research Fund, New York, N.Y.; Research Grant No. 1R01 HL16290-01A1 from the National Heart, Lung, and Blood Institute, Bethesda, Md.; the Manny Kay Fund, New York, N.Y., and the Lester and Kathlyn Wolfe Foundation Fund, New York, N.Y.

Address for reprint requests: Ira Nathan, Ph.D., Department of Surgery, New York University Medical Center, 550 First Avenue, Room H570, New York, N.Y. 10016.

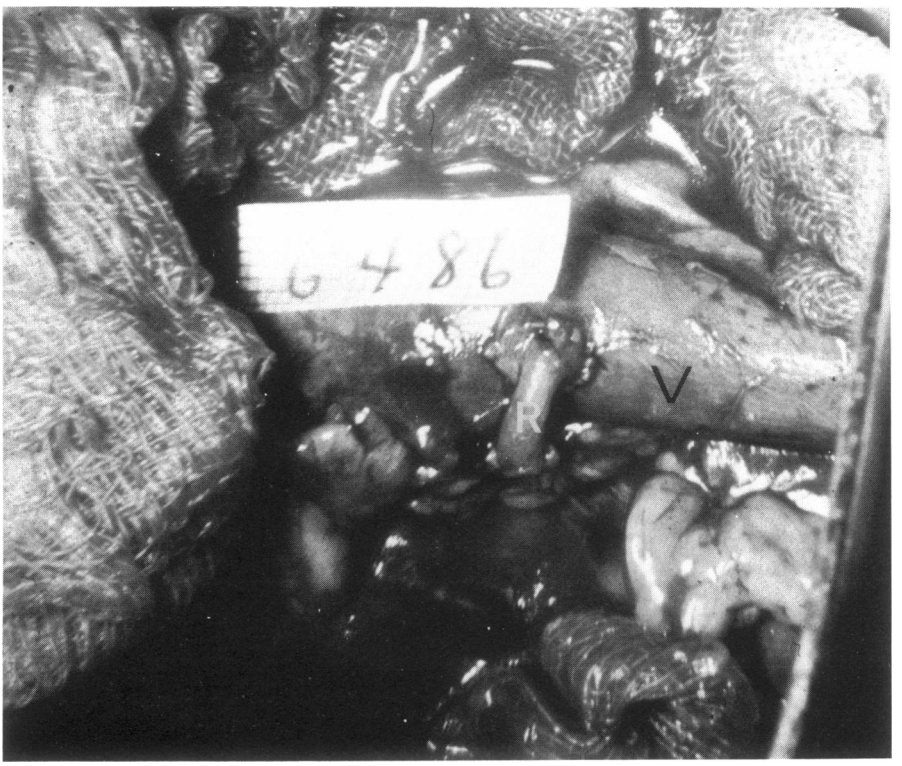

Fig. 1. Typical renal artery-vena cava junction. Note large flange of tissue on renal artery (R) at anastomosis to vena cava (V). The size of vessels can be inferred from the 1 mm. lines shown on graph paper.

shedding and platelet adherence to exposed subendothelial intima call forth migration of smooth muscle cells.

Our observations do not support this view,[9] but suggest that any of the three phenomena, observed almost simultaneously in experimental animals, could be the initiating mechanism since smooth muscle cell migration begins even before endothelial shedding has occurred, and fragmentation of the internal elastic lamella is associated with passage of smooth muscle cells through these defects. A signal or message related to specific flow patterns has been suggested to have a role in evoking the cellular proliferation originally thought to be from the intima, but which is now understood to originate from the media.[10] The intimal lesions occur in a variety of experimental models, some with accelerated flow, others with

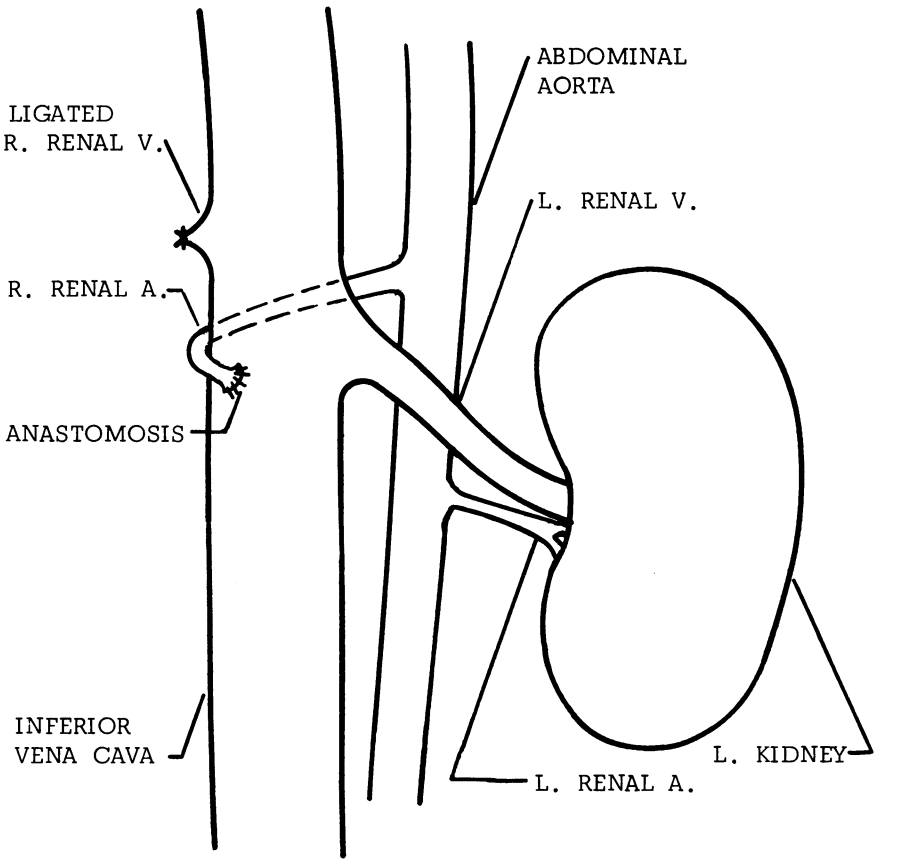

Fig. 2. Schematic representation of aortocaval shunt. Only the distal third of right renal artery was disturbed during preparation. L= left, R= right, A= artery, V= vein.

disrupted flow as may occur within a cul-de-sac. In one of the most productive models, an arterial graft was interposed between the side of the aorta and the side of the inferior vena cava, and palpable thrills and strong bruits were noted. The character of the palpable thrills and recordable sounds was found to correlate with the occurrence of lesions at stereotyped locations. The characteristics of the sound and its correlation with the lesions is the subject of this report.

Material and Methods

Male mongrel dogs weighing between 12 and 18 kg. received

laparotomies under sterile conditions and pentobarbital anesthesia (30 mg./kg.). In 31 dogs the right kidney was removed after tying off the right renal vein close to the vena cava and dissecting free and clamping the distal third of the right renal artery. The artery was cut at its bifurcation immediately proximal to the kidney and the surplus vascular tissue of the bifurcation provided a large flange for end-to-side anastomosis to the lateral wall of the vena cava. The adventitia of the vena cava was minimally dissected in preparing the site. The remaining two thirds of the renal artery and the contralateral kidney and vessels were undisturbed. The anastomosis was sutured with 6-0 Tevdek (a suture material) in a continuous everting mattress stitch to minimize internal discontinuities on which thrombi might form. Before completion, vessels were flushed by temporarily releasing the clamps and rinsing with saline solution. The right renal artery remained clamped for approximately one hour during a typical procedure. Figure 1 illustrates a typical renal artery-vena cava junction. Figure 2 is a schematic diagram of the preparation.

When vessels were unclamped, the large difference in arteriovenous pressure accelerated flows through the fistula. Preoperative and postoperative flows were measured in several dogs with an electromagnetic flow meter. Postoperative flows were two to four times as large as preoperative flows. Patency of the fistula was documented by strong bruits, a palpable thrill, and arterial and venous flow visible through the wall of the vena cava. Sound recordings of the pulsatile flow further confirmed patency, and the volume of sound was a gross measure of the viability of the shunt.

Flow sounds were transcribed with a magnetic tape recorder immediately after shunts were opened.* The sounds were transduced by a sensitive condenser microphone to which was mounted an extension probe, a 2 mm. stainless steel tube 7 cm. long.† The entrapped air column acoustically coupled the microphone to the vascular surface as long as the interface between the tube and vessel was sealed by wetting the surface with saline solution or blood. It has been shown that intraluminal vibrations can be picked up from the surface of an arterial wall by fluid contact.[11] The probe was autoclaved before each recording to provide a sterile barrier between animal and equipment. Sounds were recorded for 10 seconds each at a number of locations on the vena cava and the exposed shunt.

*Stellavox SP-7 portable synchronous tape recorder from Gotham Audio Corp., New York, N.Y.
†Bruel and Kjaer Type 4134 precision condenser microphone and type 2619 preamplifier and extension probe from B and K Instruments, Inc., Cleveland, Ohio.

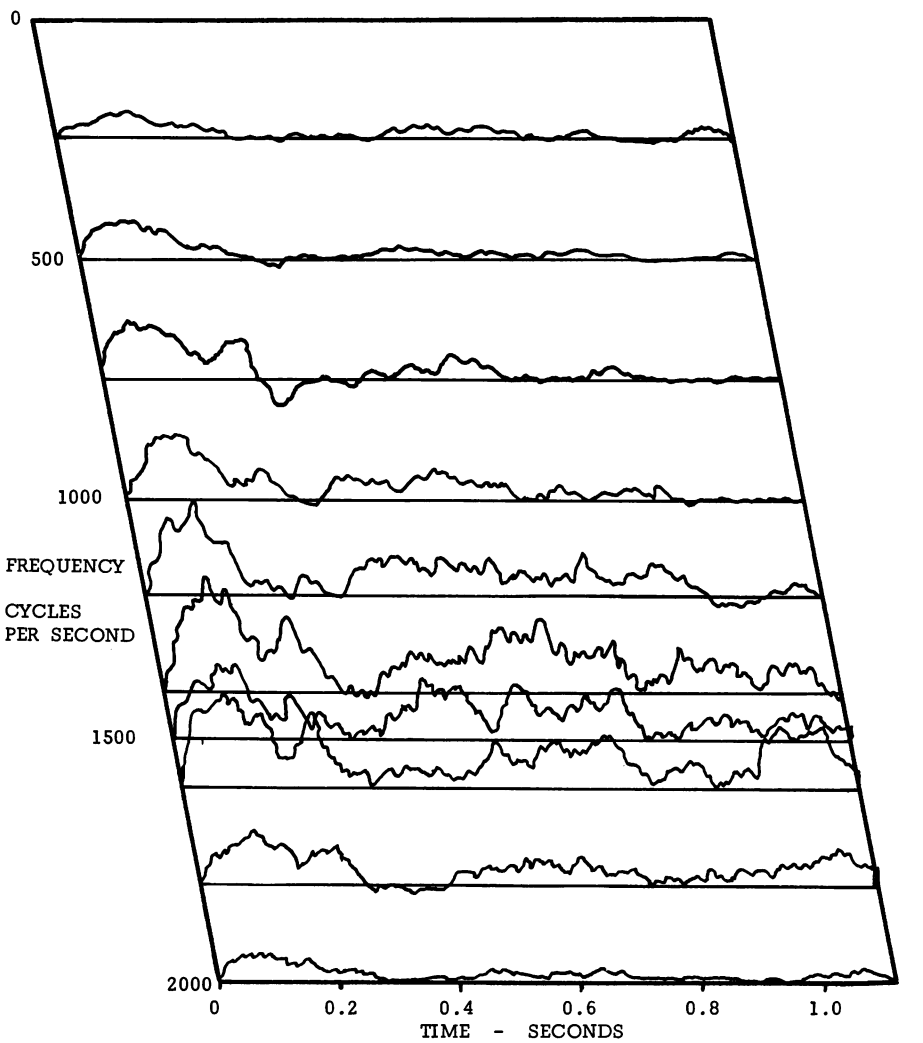

Fig. 3. Narrow-band filtered sound recorded at the anastomosis of the renal artery to the vena cava. Sound energy in relation to time is given for discrete filter frequencies. Each tracing represents a filter 100 Hz. wide.

After flow sounds were recorded, preparations were photographed and the abdomens were closed. Dogs were kept alive for from 30 minutes to 43 weeks to study anticipated histologic changes. Patency of the long-term aortocaval shunts was checked periodically by drawing blood from above and below the anastomoses through catheters which penetrated the femoral

vein and entered the vena cava. Oxygen tensions of the specimens were measured, and clear increases in the superior specimens were taken as evidence of patency. Animals in which no patency was found were killed forthwith. Tissues were fixed during killing by total perfusion of the animal with fixative, and specimens were prepared for examination by light and electron microscopy. Results of these examinations are reported elsewhere;[10] this report is concerned only with sound characteristics and the appearance of lesions.

After transcription, sounds were analyzed to determine their fundamental frequencies. Energies at specific frequencies were separated from the total sounds by passing transcribed sounds through a narrow-band filter.* By repetitious filtering at successively higher frequencies a family of tracings was developed (shown in Figure 3), which surveys a single pulse beat. The bands are approximately 100 Hz. (cycles per second) wide at the center frequencies indicated. The complete family of tracings constitutes a continuous surface whose height above the time-frequency plane indicates the sound energy at the time and frequency of its coordinates. A section through the surface would trace energy distribution as a function of frequency at a specific time. Analysis of a complex wave (the total sound) into its component frequencies also is known as Fourier analysis.

The sound processing described above was modified to produce simpler, more useful data. Transcribed sound was filtered simultaneously through 200 parallel-band pass filters in an apparatus called a real time analyzer.† Instantaneous spectra of the range of frequencies could be surveyed in 0.040 seconds, i.e., surveys could be repeated 25 times each second, and as the total sound changed the instantaneous spectra changed. The analyzer was set up to add the successive energy values in each filter as extracted from the transcription of sounds at one location for 10 seconds. By integrating so large a number of acoustic spectra, anomalous or artifact signals were averaged out, as was random noise. Further, the resulting summary of frequency spectra was not sensitive to a specific time in the pulse cycle. A typical summary spectrum is shown in Figure 4.

Supplementing the study of high-flow shunts, a second series of male mongrel dogs was prepared as models of disrupted flow. In this model, flow through the artery was prevented by distal ligation of the vessel

*Bruel and Kjaer Type 2107 Narrow Band Frequency Analyzer from B and K Instruments, Cleveland, Ohio.

†Saicor SA-51 Real Time Spectrum Analyzer-Digital Integrator from Signal Analysis Operation, Honeywell, Inc., Denver, Col.

TABLE I. CHARACTERISTICS OF 31 MALE MONGREL DOGS* AT VARIOUS PERIODS AFTER CREATION OF AORTOCAVAL SHUNTS: PRESENCE OF HIGH OR LOW FREQUENCY SOUNDS AT FISTULIZATION, PRESENCE OR ABSENCE OF PATENCY AT DEATH, CHARACTERISTICS OF LESIONS, PRESENCE OR ABSENCE OF THROMBI (T), AND INTERVAL BETWEEN SHUNTING AND DEATH.

	Low frequency		*High frequency*	
Lesions	*Patency*	*No patency*	*Patency*	*No patency*
Symmetrical		4 wk. (1) T 5 wk. (1) T 6 wk. (1) T 10 wk. (1) T 11 wk. (1) T 13 wk. (1) T 13 wk. (1) 30 wk. (1) T	10 wk. (1) T	
Asymmetrical			2 hr. (1) 1 wk. (5) 2 wk. (1) 8 wk. (1) 16 wk. (1) 24 wk. (1) 43 wk. (1)	
Symmetrical and asymmetrical		1 hr. (1) T	15 wk. (1)	4 wk. (1) 10 wk. (1) 13 wk. (1) 16 wk. (1) 17 wk. (1) T 23 wk. (1)
None	17 wk. (1)	30 min. (1) T 12 wk. (1) T		

*Number of dogs is given in parentheses.

chosen for study, but proximal communication with the primary blood supply was maintained. Thus, a renal artery which is ligated distally would undergo pressure pulses and would receive a miniscule reentry flow, mixing, and departing flow into its cul-de-sac configuration. Similarly, ligated carotids, abdominal aortas, iliac, and splenic arteries were models for disrupted flow. Complete stasis of flow was never imposed, nor was the model vessel isolated from arterial pressure. In some animals several arteries were ligated simultaneously. In none of the disrupted flow preparations was there recordable sound. After varying time periods, these animals were killed as described above and vascular tissues were prepared for light and electron microscopy.

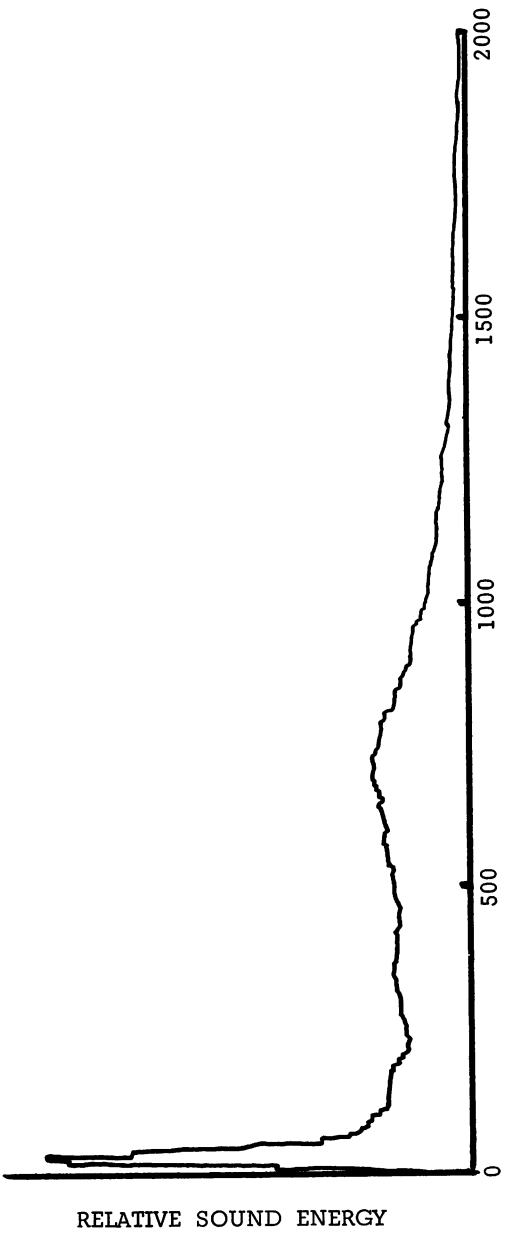

Fig. 4. Frequency distribution of sound energy recorded at a single site of the anastomosis of the right renal artery to inferior vena cava integrated during 10 seconds. No significant energy is shown at high frequencies.

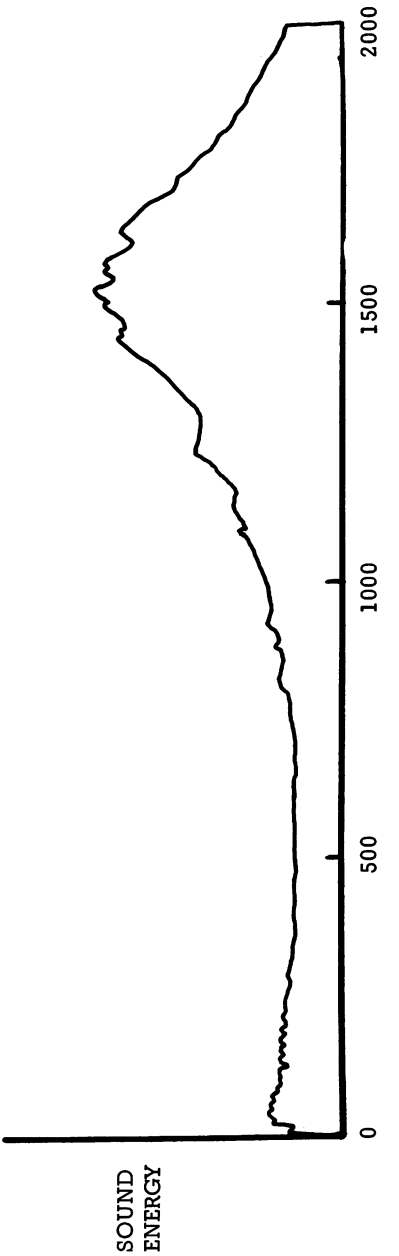

Fig. 5. Frequency distribution of sound energy recorded at a single site of the anastomosis of the right renal artery to inferior vena cava, integrated during 10 seconds, illustrating high-frequency energy.

Results of Shunting

Observations of the 31 dogs used in the study of shunted flow are listed in Table I. Auditory and histological characteristics were classified independently and designation of animals for killing was random. The identifying criteria by which all subjects were classified are delineated in Table I: presence or absence of high-frequency sounds at time of fistulization, presence or absence of patency at the time of death, type of lesion (symmetrical or asymmetrical), and the presence or absence of thrombi. The time interval between creation of the shunt and death is also shown.

Sound. Sounds of flow were analyzed for frequencies to 5,000 Hz., but negligible energy appeared above 2,000 Hz. All analyses, therefore, were between 0 and 2,000 Hz. in 200 bands of 10 Hz. each. Within this range sounds were classified arbitrarily as containing high-frequency energy if significant peaks occurred above 1,000 Hz. and as containing low-frequency energy if such peaks were not present. Some energy appeared at low frequencies in all cases studied. Figure 4 shows a typical low-frequency spectrum in contrast with Figure 5, which shows a high-frequency spectrum. Sounds could not be segregated by the human ear, although some high-frequency recordings presented a high-pitched squeak. Other recordings masked the high-frequency sounds under a bass rumble; electronic analysis uncovered the high-frequency components.

Patency. At the time of preparation all shunts were patent, as evidenced by pulsatile flow sounds, a palpable thrill in the vena cava, and visible mixing of arterial blood with venous blood which was clearly seen through the thin caval wall. At the time of death, however, vessels were considered not patent if all three indicators were missing. Although near-total occlusion could obliterate sounds and bruit, arterial blood might be seen if dissection to the vena cava were possible. Unfortunately, massive tissue reactions and adhesions impeded access to the vena cava, and the initial assessment of nonpatency based upon lack of sounds or thrill was reversed only after microscopic examination showed a passage—often severely reduced—through the renal artery. In some near-occluded shunts, flow sounds were present only during inspiration, i.e., during periodic intervals of reduced central venous pressure. Blood-gas tests to determine patency were similarly misleading. Indications of nonpatency often were contradicted by microscopic examination, possible because blood specimens were drawn at times when arterial blood was transiently absent.

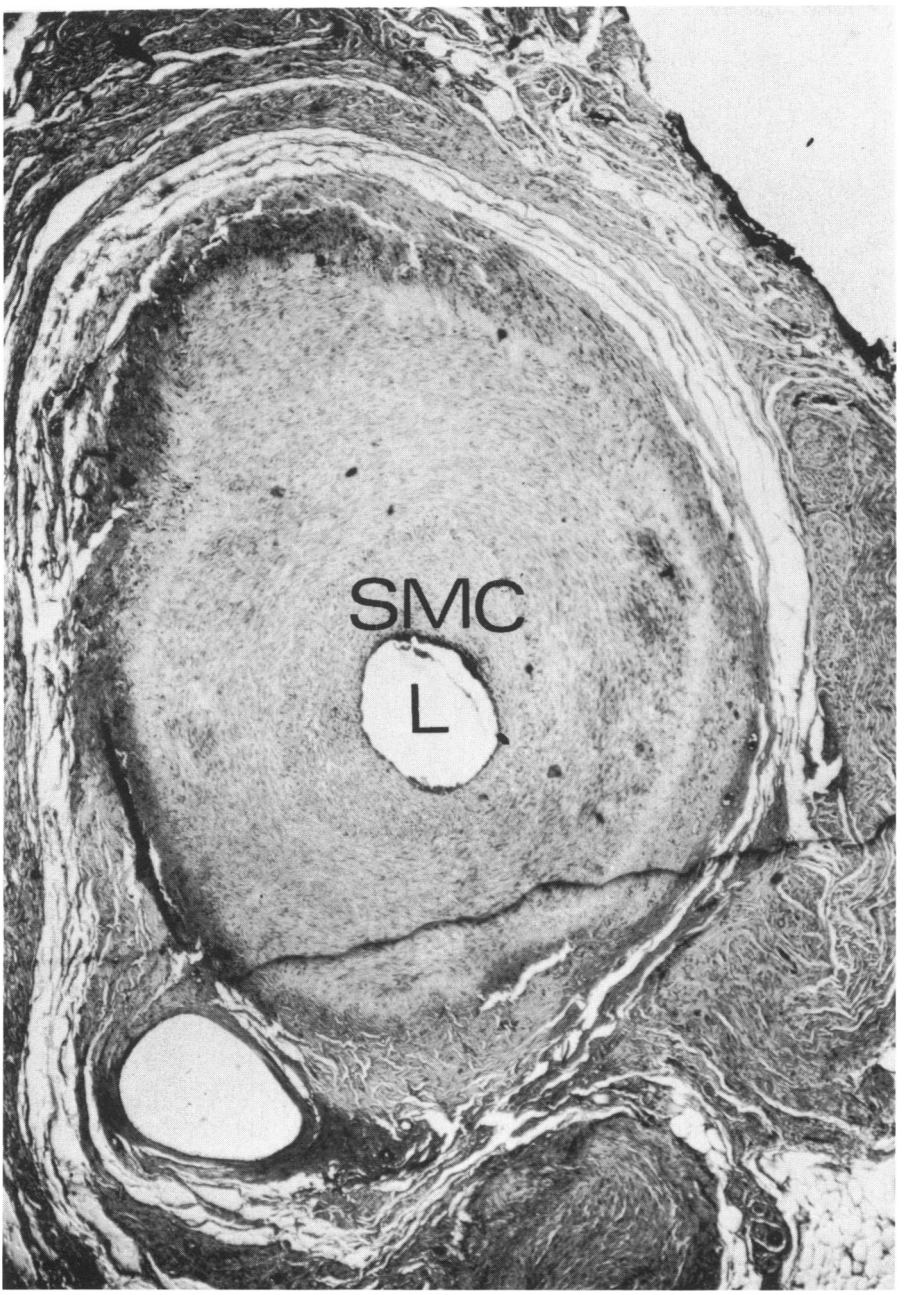

Fig. 6. Photomicrograph of section of renal artery in which a symmetrical lesion of smooth muscle cells (SMC) has substantially reduced the lumen (L).

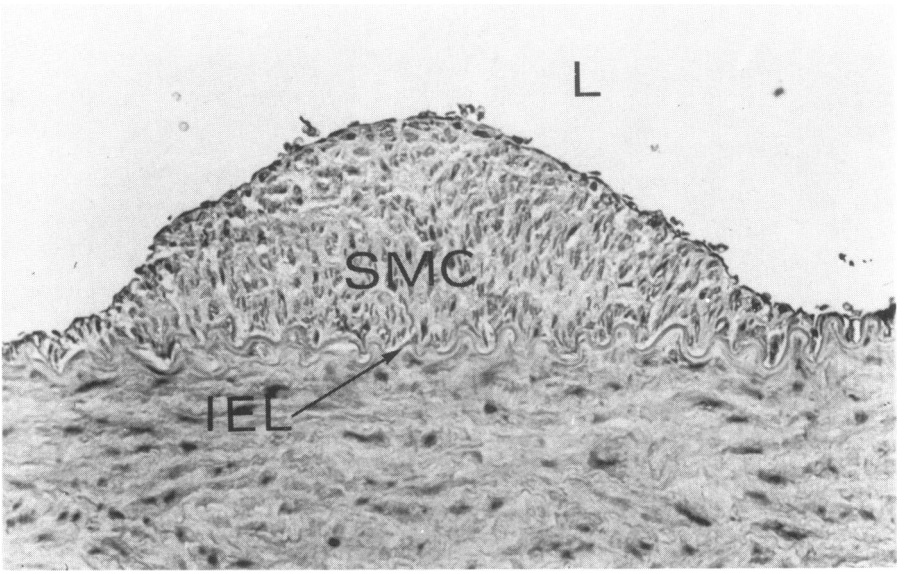

Fig. 7. Photomicrograph of a section of renal artery in which a highly localized asymmetrical lesion of smooth muscle cells (SMC) protrudes into the lumen (L). Note that the smooth muscle cells lie on the intimal side of the internal elastic lamina (IEL).

Lesions. The incidence of lesions in the dogs with shunts is summarized in Table I. By examination of sections of vessel, lesions were characterized as concentric or symmetric versus asymmetrical. Symmetrical lesions thickened the intima around the entire circumference at a section and intruded into the lumen, as illustrated in Figure 6. Asymmetrical lesions were highly localized, appearing on a limited length of the vessel and at a limited segment of the circumference, as shown in Figure 7. Concentric lesions generally appeared at the distal end of the renal artery with thinner development proximally. Asymmetrical lesions developed in the vicinity of the aortic ostium and in the vena cava near the anastomosis and on the wall opposite, as shown in Figure 8.

In eight cases, symmetrical and asymmetrical lesions appeared in the same animal at different locations in the renal artery. Three animals had no apparent lesions, although the shunts in two were occluded by thrombi. Vessels in the unscarred animal remained unexplainably patent for 17 weeks.

All animals with symmetrical lesions which had shown no high-

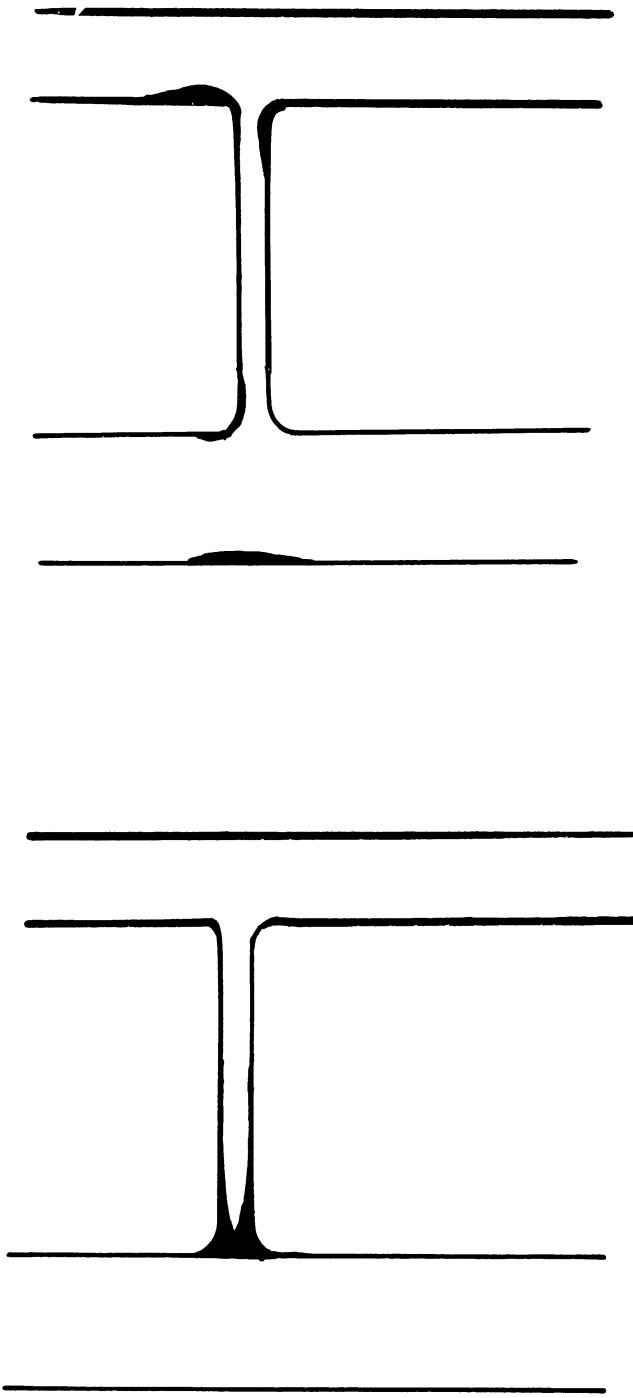

Fig. 8. Schematic representation of locations of lesions in symmetrical (left) and asymmetrical (right) configurations.

frequency sounds had vessels which were not patent, whereas asymmetrical lesions were associated with high-frequency sounds and were in shunts found patent at time of death. Most of the animals with both types of lesions had vessels which were not patent, but had shown high-frequency sounds at set-up. Because asymmetrical lesions are associated with flow and patency, we assume that where both lesions occurred the asymmetrical lesions developed first until thrombi blocked the flow, and thereafter symmetrical lesions developed.

Thrombus. Thrombi were found in all vessels which were not patent (except one) in which symmetrical lesions and low-frequency sounds were found. The thrombus was always located at the distal end of the renal-artery shunt; the two lesion-free animals were occluded at the same location. Of the nonpatent specimens in which high-frequency sounds were noted at set-up, a thrombus appeared in only one shunt, whereas five shunts were free of thrombi. These preparations showed symmetrical and asymmetrical lesions. Needless to say, no thrombus appeared in patent vessels.

It appears that in some animals symmetrical lesions partially occluded the flow, and subsequent thrombi formed to complete the blockage. In such instances a clear demarcation could be seen between the lesion and thrombus. However, in other instances initial blockage by a thrombus led to the typical lesion growth. The thrombus reorganized and simulated the balance of lesion structure, but the division between lesion and thrombus was indistinct. The remains of red cells from the thrombus were found entrapped in the lesion.

Time of preparation. The animals of this study were maintained between 30 minutes and 43 weeks. The time obviously was not related to the initially noted frequencies, but it affected neither the distribution of thrombosed shunts nor the types of lesions. Because of the inconclusiveness of blood-gas checks made on many of the dogs, those without patent vessels could have had early failure or even initial closure immediately after surgery. Blood-gas tests every four to six weeks could not screen early initial failures, although direct observations of fistulae were made during the recording of sounds. The uncertainty of catheter locations relative to the shunt anastomoses also caused blood-gas tests to be uncertain. Some animals may have been kept alive long after their shunts closed.

TABLE II. CHARACTERISTICS OF 21 MALE MONGREL DOGS*AT VARIOUS PERIODS AFTER LIGATION OF VESSELS: PRESENCE OF THROMBI, PRESENCE OF LESIONS, TYPE AND LOCATION OF LESIONS, AND INTERVAL BETWEEN LIGATION AND DEATH.

Location	*Thrombi*	*Symmetrical lesions*	*Asymmetrical lesions*	*No alterations*
Carotid artery	2 hours (1) 3 hours (2) 2 days (1) 4 days (1) 5 days (1) 6 days (1) 7 days (1) 28 days (1)		2 hours (1) 3 days (2) 4 days (1)	2 hours (1) 5 days (1) 30 days (1)
Renal artery	7 days (1)	30 minutes (1) 35 days (1)	2 hours (5) 21 days (1)	2 hours (2) 5 days (1) 14 days (1)
Aorta			2 hours (1) 3 days (1) 7 days (1) 30 days (1) 35 days (1)	
Iliac artery	35 days (1)	21 days (1) 35 days (1)	7 days (1) 14 days (1)	3 days (1)
Splenic artery				30 days (1)

*Number of dogs is given in parentheses. Many dogs had multiple ligations.

RESULTS OF LIGATION

Observations of the 21 dogs with ligated vessels are summarized in Table II. Tissues were characterized by three findings: presence of extended thrombi, presence of lesions, and type of lesions. The time interval between creation of the shunt and death also is shown.

Presence of extended thrombi. All prepared vessels showed thrombi in the immediate vicinity of the ligature, both proximally and distally. However, in some preparations the thrombus extended through the length of the vessel, completely filling its lumen with clot. This occurred in most of the carotid-artery preparations, one renal artery, and one iliac artery. The phenomenon was independent of time, occurring in preparations of from two hours to 35 days survival, although the time at which the thrombi formed cannot be specified.

Presence of lesions. Sections of vessel from beyond the region of near-ligature thrombus were examined for intimal hyperplasia. Lesions

were found in carotid and renal arteries, aortas, and iliac arteries, but, surprisingly, three of the carotid models, four of the renal models, and a splenic artery had no lesions. This unexpected result appeared to be independent of time, and these vessels had no extended thrombus.

Type of lesion. Vascular tissues with lesions were classified as symmetrical or asymmetrical as previously described. As indicated in Table II, lesions were primarily of the asymmetrical or focal type, although several symmetrical lesions were noted in ligated renal and iliac arteries. No time dependence was noted.

Discussion

It was realized in the development of experimental models for the production of intimal hyperplasia that the occurrence and location of lesions was characteristic for each model. High-flow models, such as anastomosis of the right renal artery to inferior vena cava, interposition of the carotid artery between the aorta and inferior vena cava, and anastomosis of the distal cut end of the iliac artery to the iliac vein resulted in the formation of lesions in the first and second but not in the third model. Characteristically, lesions correlated with the finding of high frequencies in the analysis of sound patterns. The analysis of the sounds of the iliac artery did not show the characteristic frequencies which usually are associated with the formation of lesions.

In states which do not involve high flow, such as ligation of major arteries and early thrombosis of aortocaval shunts in which lesions developed, no sounds of any type could be recorded.

The possible biologic activity of sound is unproved. Its existence is suggested by its effect on tissues of the vascular wall and its effect on blood fluids. With regard to the structure of vascular wall tissue, a number of studies have been made on sound and the origins of poststenotic dilatation;[12,13] the murmurs produced by the stenosis have been implicated and specific frequencies have been identified. The murmur-associated vibrations induce repeated flexure of elastin fibers in the vessel wall and ultimately cause "fatigue failure," a cumulative breakdown evidenced by the dilatation. Under no-flow conditions *in vitro* arteries were stimulated by pure sine-wave pressure oscillations, and resonant frequencies which fell within the range of pressure disturbances of turbulent flow were found for the vessel.[14] These experiments indicate a clear connection between abnormal flow-induced sound and a tissue-breakdown response.

In a separate study, alteration of metabolic processes in tissues has been associated with an oscillatory stimulus.[15] During tissue culture arterial smooth muscle cells were affixed to a substrate which could be mounted in a stretching rig. The substrate and attached cells were cyclically stretched and relaxed in this rig, while control specimens attached to the same substrate in the same environment remained at rest. The cycled cells produced significantly more collagen and other matrix components than the cells at rest. The cyclic stress of elongation is not dissimilar to the stress of acoustic or oscillatory pressure.

The biological activity of sound as expressed through vibrations of the blood itself has been studied by Michal,[16] who induced aggregation with acoustic vibration of very low energy. He determined that the bombarded platelets were induced to release thrombogenic materials, including adenosine diphosphate and 5-hydroxytriptamine. Goldsmith[17] forced blood to flow in tubes in an oscillatory mode. When the blood was oscillated in the presence of thrombin he found accelerated release of platelet serotonin. Others[18-20] have studied the tolerance to shear of red blood cells and measured the shear forces present in anomalous blood flow. The reactions found in our own animal models, thus, might be related to mechanisms in the blood itself, to mechanisms in the vessel wall, or to some unidentified interaction between them.

The origins of sound in blood flow have been the subject of considerable speculation, theorization, and *in vitro* and *in vivo* study. Certain principles do have general acceptance: Sound does not originate in laminar flow, but is only generated in the presence of disturbed or turbulent flow.[21] Turbulence, alone, however, does not assure the generation of sound, and when fully developed turbulence does generate sound through shear and eddies, it produces a "gray" noise, a nearly uniform frequency distribution associated with the randomness of eddy formation. Sound also is related to the instabilities of flow, and these tend to express themselves in discrete frequencies. One such instability, the generation of vortices, is credited by Bruns[22] with the production of specific frequencies, Aeolian tones which were first described by Von Karman as the vortex street.[23] Murmurs and Korotkoff sounds originate in instabilities of flow or walls occurring as surfaces resonate or fluid detaches and reattaches at specific frequencies.[24] Our study is not concerned with the origins of the sounds noted. In the context of this model, the sounds are ubiquitous, being transmitted from wherever they originate to every point through tissue and fluid transmission.

The primary result of this study is summarized in Table I: the association of low-frequency sounds with vessels occluded by thrombi and symmetrical lesions, and the association of high-frequency sounds with the absence of thrombi, unobstructed flow, and asymmetrical lesions. The apparent contradiction, the development of lesions under circumstances which do not produce sound audible to the equipment, suggests four possible conclusions:

1) Sound is in no way related to atherosclerosis.

2) Sound is generated which significantly affects tissues, but is externally inaudible.

3) Atherogenesis is triggered by the absence of specific frequencies.

4) Other phenomena cause the tissue response and sounds in moving flow.

Regarding the first possibility, the data in Table I are too strong to set aside as the result of random distribution. Chi-square analysis of the frequency/symmetry distribution shows that the pairing of high frequency and asymmetrical lesions is highly significant ($p<0.005$).

As to the second possibility, it is conceivable that instabilities in flow are created in other vessels by the experimental ligation of certain vessels. Thus, elimination of renal flow, for example, could cause detachment phenomena in the aorta.[25] Carotid ligation, similarly, could alter flow in the aortic arch, and ligation of the aorta forces redistribution of flow to the lumbar arteries and other branching vessels. The disturbance of flow passing the entry to the ligated vessel could cause pressure oscillations or reverberations to travel to the closed end and to be reflected at a specific frequency, similar to the way tone is generated in an organ pipe. Because energy in the disturbed flow would be low, the amount to escape, i.e., to be externally audible, would be insignificant.

Regarding the third alternative, normal flow which is not atherogenic may have sound components which are biologically requisite for vessel-wall stability. The high-velocity flow may obliterate such sounds, thereby triggering atherogenesis. In the model of disrupted flow, the necessary sounds also would be missing.

As to the fourth possibility, if the relations of Table I are valid it may be assumed at the least that the frequency-specific sounds are produced by some property of the flow (such as velocity, velocity gradient, separated flow, or flow impingement), by some property of the vessel wall (such as surface roughness, altered elasticity, or geometric anomaly), or by some

property of the blood (such as heterogeneity, altered stickiness, surface charge of cell membranes, or blood-cell location or orientation) which promotes the generation of lesions. In the ligation model some of these properties might develop and, although they do not generate sound, they may initiate atherogenesis.

The second and third alternatives are consistent with the suggestions of Imparato[9] and Wesolowski[6] that lesions may be produced by critical injury in the walls as the result or absence of specific vibrations. Short-term response to the shunted vessels is evidenced in deep tissues which are not in direct contact with the flowing blood. This suggests that a signal has been transmitted to evoke such a response; the signal may be related to the presence or absence of some frequency of the pressure oscillations in the blood flow.

Further study of sound in blood flow may provide better insights into the processes whereby atheroma begin to form. Relations have been uncovered, but contradictions abound. In their resolution the origins of atherosclerosis may be found.

REFERENCES

1. Imparato, A. M., Lord, J. W., Jr., Texon, M., and Helpern, M.: Experimental atherosclerosis produced by alteration of blood vessel configuration. *Surg. Forum 12*:245-47, 1961.
2. Ross, R. and Glomset, J. A.: The pathogenesis of atherosclerosis. *N. Engl. J. Med. 295*:369-77, 420-25, 1976.
3. Spaet, T. J., Gaynor, E., and Stemerman, M. B.: Thrombosis, atherosclerosis and endothelium. *Am. Heart J. 87*:660-68, 1974.
4. Caro, G. G.: Transport of material between blood and wall in arteries. *Ciba Found. Symp. 12*:127-48, 1973.
5. Texon, M.: The hemodynamic basis of atherosclerosis. *Bull. N.Y. Acad. Med. 48*: 733-40, 1972.
6. Wesoloski, S. A., Fries, C. C., Sabini, A. M., and Sawyer, P. N.: The significance of turbulence in hemic systems and in the distribution of the atherosclerotic lesion. *Surgery 57*:155-62, 1965.
7. Duguid, J. G.: Pathogenesis of arteriosclerosis. *Lancet 2*:925-27, 1949.
8. Gutstein, W. H. and Schneck, D. J.: *In vitro* boundary layer studies of blood flow in branched tubes. *J Atheroscl. Res. 7*:295-99, 1967.
9. Imparato, A. M., Bracco, A., Hammond, R., Kaufman, B., Kim, G. E., Magrassi, P., Pearson, W., Baumann, G., and Nathan, I.: The effect of intimal and neointimal fibroplasia on arterial reconstructions. *J. Cardiovasc. Surg. 14*:488-94, 1973.
10. Imparato, A. M., Baumann, F. G., Pearson, J., et al.: Electron microscopic studies of experimentally produced fibromuscular arterial lesions. *Surg. Gynecol. Obstet. 139*:497-504, 1974.
11. Boughner, D. R., and Roach, M. R.: Effect of low frequency vibration on the arterial wall. *Circ. Res. 29*:36-44 1971.
12. Roach, M. R.: An experimental study of the production and time course of

poststenotic dilatation in the femoral and carotid arteries of adult dogs. *Circ. Res. 13*:537-51, 1963.
13. Roach, M. R., and Melech, E.: The effect of sonic vibration on isolated human iliac arteries. *Can. J. Physiol. Pharmacol. 49*:288-91, 1971.
14. Foreman, J. E., and Hutchinson, K. J.: Arterial wall vibration distal to stenoses in isolated arteries of dog and man. *Circ. Res. 26*:583-90, 1970.
15. Leung, D. Y. M., Glagov, S., and Mathews, M. B.: Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro. *Science 191*:475-77, 1976.
16. Michal, F.: Platelet aggregation by very low intensity accoustical energy and its inhibition by drugs. *Proc. Brit. Pharmacol. Soc. 40*:544-45, 1970.
17. Goldsmith, H. L.: The effects of flow and fluid mechanical stress on red cells and platelets. *Trans. Am. Soc. Artif. Intern. Organs 20*:21-26, 1974.
18. Yu, S. and Goldsmith, H. L.: Behavior of model particles and blood cells at spherical obstructions in tube flow. *Microvasc. Res. 6*:5, 1973.
19. Blackshear, P. L., Jr., Forstrom, R. J., Dorman, F. D., and Voss, G. O.: Effect of flow on cells near walls. *Fed. Proc. 30*:1600, 1971.
20. Goldsmith, H. L.: Red cell motions and wall interactions in tube flow. *Fed. Proc. 30*:1578, 1971.
21. McDonald, D. A.: *Blood Flow in Arteries*. London, Arnold, 1960, 69 ff.
22. Bruns, D. L.: A general theory of the causes of murmurs in the cardiovascular system. *Am. J. Med. 27*:360-74, 1959.
23. Von Karman, T.: Turbulence: *J. Royal Aeronaut. Soc. 41*:1109, 1937.
24. Anliker, M. and Raman, K. R.: Korotkoff sounds at diastole — a phenomenon of dynamic instability of fluid-filled shells. *Int. J. Solid Struct. 2*:467, 1966.
25. Rockwell, D.: Prediction of oscillation frequencies for unstable flow past cavities. Paper 76-WA/FE-17. *Am. Soc. Mech. Eng. Winter Annual Meeting*, December 1976.